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MEDICAL STAFF CONFERENCE

Hypersplenism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* For centuries the spleen has been an enigmatic organ, often the seat of disease but of uncertain function. More recently new insights have been obtained concerning its role in the homeostasis of hemic cells. It has long been said that we shall understand hypersplenism only when we understand "splenism." We have asked Dr. Curt A. Ries, Assistant Clinical Professor of Medicine and Clinical Pathology and Laboratory Medicine, to discuss the pathophysiology of excessive splenic function. A subsidiary and very practical question is: How can we determine when a given patient will benefit from splenectomy? Dr. Ries, please clarify the post-Banti era for us.

DR. RIES:† The association of splenomegaly with reduction of one or more of the circulating blood cells has been known for more than a century. In 1866 Gretsel described the association between splenomegaly and certain types of anemia, which he termed *splenic anemia.*[1] In 1882 Banti published his first description of the association between anemia and splenomegaly, and began a series of experiments demonstrating the pathogenic relationship between the enlarged spleen and the anemia.[2] Banti also described leukopenia in patients with enlarged spleens and noted that frequently these patients died with cirrhosis of the liver. He was the first to question the mechanism of splenic cytopenias, that is, whether the enlarged spleen reduces peripheral blood cell counts by destroying circulating blood cells or by releasing humoral factors which suppress production or release of the blood cells from the bone marrow. Banti also encouraged experimentation with splenectomy in human diseases characterized by splenomegaly and blood cytopenia. Sir Spencer Wells performed the first known therapeutic splenectomy for hemolytic anemia, in 1887.[3] In 1907 Chauffard coined the term hypersplenism, a term which is generally accepted today.[4]

Opinions differ as to what categories of diseases should be included within the definition of hypersplenism. I believe it is useful to define hypersplenism in a functional sense, that is, as those conditions where it is known, either from clinical experience or by kinetic studies using radioactively labeled blood cells, that the spleen is the major site of blood cell destruction and that the peripheral blood cytopenia will be corrected by splenectomy. I define hypersplenism, then, as anemia, leukopenia, thrombocytopenia, or a combination of these resulting from excessive splenic sequestration or pooling of blood cells, usually as-

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.
†Curt A. Ries, M.D., Assistant Clinical Professor of Medicine, and Clinical Pathology and Laboratory Medicine.

TABLE 1.—*Hypersplenism: Anemia, Leukopenia, Thrombocytopenia, or a Combination of These Resulting from Excessive Splenic Sequestration or Pooling of Blood Cells, Usually Associated with Clinical Splenomegaly and Always Ameliorated by Splenectomy*

—Resulting from splenic enlargement (congestion, infiltration, infection)
—Resulting from intrinsic defects of blood cells (hereditary spherocytosis, sickle cell anemia)
—Resulting from autoimmune destruction of blood cells (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura)

sociated with clinical splenomegaly and always ameliorated by splenectomy.

Hypersplenism can be divided into three categories (Table 1). The first, hypersplenism resulting from splenic enlargement, is perhaps the most common and best known category. It is the only true hypersplenism—that is, the only instance in which primary changes in the spleen or splenic circulation are solely responsible for excessive destruction of blood cells. Splenic enlargement, when it occurs in the other two categories, is a result of a primary abnormality of the blood cells themselves, or of the interaction of blood cells with humoral factors, leading to abnormal sequestration and destruction of these cells by the spleen. Some investigators do not include these latter two categories within the definition of hypersplenism because the spleen is performing its normal physiologic function, and splenic sequestration is a secondary response to the presence of damaged blood cells in the circulation. I believe it is useful to include these latter two categories, however, since they are cytopenias which in most instances are caused by increased destruction of blood cells in the spleen and are completely ameliorated by the splenectomy.

Ever since the work of Banti in the latter part of the Nineteenth Century, there has been a great deal of interest in the mechanism of hypersplenism. There are at least two possible mechanisms: (a) that the spleen produces humoral factors which suppress production or release of blood cells from the bone marrow, or (b) that the spleen causes cytopenias by excessive pooling, sequestration, or both, and ultimate destruction of the circulating blood cells. Most clinical observations and experimental work support the second hypothesis. There are several lines of evidence for this conclusion. First, the bone marrow of patients with hypersplenism usually shows hyperplasia of the precursors of the cells that are decreased in the peripheral blood. Recent kinetic studies using isotopically labeled blood cells confirm these morphologic observations by demonstrating increased cell destruction with splenic sequestration, and a compensatory increase in production of the involved cell lines by the bone marrow.[5-14] Second, direct counts of blood cells from splenic artery and vein have demonstrated cell density gradients across the splenic circulation in experimental animals and in patients with hypersplenism.[15] Clearly, the reduction in cell density observed in splenic venous blood can be directly attributed to splenic sequestration of these cells. Third, hypersplenism can be induced in experimental animals by various methods, and it can be demonstrated that the resulting cytopenias are caused by splenic sequestration and destruction of the involved blood cells.

Experimentally, one can induce splenomegaly by overloading the reticuloendothelial system by injection of poorly metabolized substances. This can be shown to result in splenic sequestration and destruction of blood cells from all cell lines and in a compensatory increase in production of blood cells by the bone marrow.[16,17] Furthermore, splenic tissue can be implanted into animals that have had splenectomy, and these implants grow and sequester blood cells. Chronic hemolysis produced by acetylphenylhydrazine increases the sequestration of red cells in the splenic implants; the splenic implant enlarges and hypersequestration of all cell lines occurs.[18] If the implant is enclosed within a Millipore diffusion chamber which has been designed to allow passage of humoral factors but not blood cells, sequestration does not occur and cytopenias do not develop.[18] Therefore, it appears from these experiments that the cytopenias develop as a direct result of the destruction of circulating blood cells in the spleen rather than as a result of bone marrow suppression by humoral factors. Because of the many similarities between experimental hypersplenism in animals and hypersplenism in human disease states, it seems quite clear that the primary mechanism causing cytopenias in hypersplenism is increased destruction of blood cells in the spleen.

During the past decade the microscopic anatomy of the spleen has been more clearly defined,

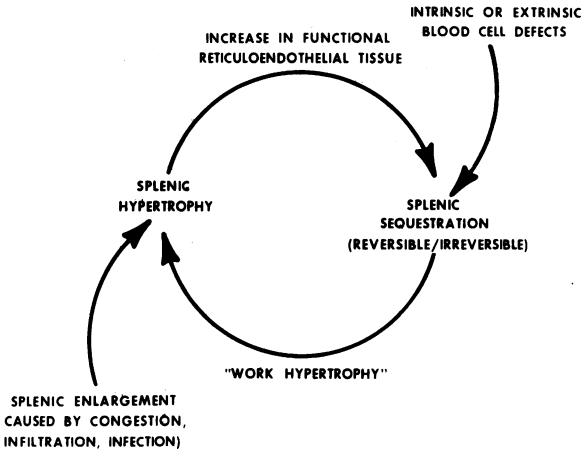

Chart 1.—Pathogenesis of hypersplenism.

resulting in a more precise understanding of the role of the spleen in filtering, remodeling, sequestration and destruction of blood cells.[19-22] The red pulp of the spleen, where these processes occur, is composed of cords and sinuses. The surfaces of these structures are lined by phagocytic macrophages and reticuloendothelial cells. The circulating blood cells enter the splenic cords from the terminal arterioles, pass through fenestrations in the basement membrane between cord and sinus and then through narrow slits between sinus endothelial cells into the sinuses, from which they exit via the splenic veins. The cord-sinus interface provides a unique screen-like filtration system through which all blood cells must pass.[21-22] Openings through the fenestrations and slits measure less than three microns in width, offering a major anatomic barrier to passage of blood cells through the cord-sinus circulation.[21-22] This implies that cell deformability—that is, the ability of blood cells to squeeze through these narrow openings—is essential to prevent abnormal sequestration and destruction of the cells in the spleen. Deformability in turn depends on a healthy, metabolically active blood cell, a pliable and functional membrane, and absence of cytoplasmic inclusions or precipitates which would prevent free flow through the small openings. Abnormal red blood cells, such as those in hereditary spherocytosis, sickle cell anemia, or Heinz body hemolytic anemias, have difficulty passing through these small openings and become trapped in the splenic red pulp.[20] Once sequestered in the spleen, these trapped cells are exposed to metabolic conditions (hypoxia, hypoglycemia, acidosis) which further limit their survival. Ultimately, the cells are destroyed by splenic macrophages and reticuloendothelial cells.

Splenic sequestration may be initiated by either primary splenic enlargement or by intrinsic or extrinsic defects in the blood cells themselves (Chart 1). Regardless of the triggering event, splenic sequestration results in "work hypertrophy" of the spleen, an increase in the functional reticuloendothelial tissue mass, further sequestration, and further splenic hypertrophy.[23] The reversibility of splenic sequestration depends on multiple factors relating to both the spleen and the blood cells themselves. These include size, shape, deformability, and metabolic status of the blood cells; variations in the metabolic environment of the spleen; changes in the size and activity of the splenic phagocytic cell mass; variations in the cord-sinus circulation; and the duration of cell sequestration in the spleen.

Hypersplenism resulting from splenic enlargement has traditionally been considered to be either primary or secondary. It is doubtful, however, whether true primary hypersplenism exists. The older terminologies of primary hypersplenism and primary splenic anemia and neutropenia probably reflect a lack of understanding of the true pathogenesis of these disorders. In the absence of demonstrable histopathologic changes in the spleen and in the absence of portal hypertension, the cytopenias previously regarded as primary hypersplenism are likely the result of either intrinsic defects in the blood cells themselves or immune cytopenias in which antibody activity has not been clearly demonstrated.

The most common causes of hypersplenism resulting from an enlarged spleen are cirrhosis of the liver with portal hypertension and congestive splenomegaly (Banti's syndrome) and neoplastic diseases of the spleen (Table 2). Hypersplenism associated with infection is rare in California, although it is a common problem in tropical countries. The connective tissue diseases and sarcoidosis frequently produce a mild to moderate degree of hypersplenism. In Felty's syndrome severe neutropenia, usually due to hypersplenism, is characteristic.

The use of radioactive labels to determine the survival and sequestration of blood cells has received increasing attention and acceptance since Jandl and associates first described the usefulness of radioactive chromium in the study of

TABLE 2.—*Causes of Hypersplenism Resulting from an Enlarged Spleen*

Congestive splenomegaly	• Cirrhosis of the liver. • External compression or thrombosis of portal or splenic veins.
Neoplastic diseases	• Lymphomas and Hodgkin's disease. • Leukemias (chronic lymphocytic leukemia, chronic myelogenous leukemia, acute leukemias). • Myeloproliferative disorders (polycythemia vera, myelofibrosis with myeloid metaplasia).
Inflammatory diseases	• Acute infections (mononucleosis, hepatitis, subacute bacterial endocarditis). • Chronic infections (tuberculosis, malaria, syphilis, kala-azar). • Sarcoidosis. • Connective tissue diseases (lupus erythematosus, Felty's syndrome).
Reticuloendotheliosis	• Lipoid type (Gaucher's disease, Niemann-Pick disease, Schuller-Christian disease). • Nonlipoid type (Letterer-Siwe disease, acute histiocytoses).

normal and abnormal red blood cell survival and sequestration in man.[5] Similar techniques are now available for the study of platelet survival and sequestration, and a great deal has been learned during the last decade regarding the kinetics of the thrombocytopenias in various clinical disorders.[8-13] Technical difficulties have limited the study of granulocyte kinetics in leukopenic states, and there is still considerable uncertainty as to the underlying defect in many of the syndromes associated with neutropenia.

In hypersplenism resulting from splenic enlargement, such as in congestive splenomegaly, anemia caused by excessive sequestration of red blood cells is usually mild to moderate. However, with massive splenomegaly such as sometimes occurs in the myeloproliferative disorders, lymphoproliferative malignancies, and some of the tropical splenomegalies, a major portion of the total red blood cell pool may be contained within the spleen. Severe anemia may occur in these conditions even when the total body red cell mass is near normal, and splenectomy is frequently of great benefit.[24] By determining blood volume with the "double blood volume" technique (^{51}Cr-red blood cell volume and ^{131}I-albumin plasma volume), together with a ^{51}Cr-red cell survival-sequestration study, one can usually successfully predict whether splenectomy will be helpful. The ^{51}Cr-red cell survival in such cases may be near normal, in spite of the fact that a major portion of the red cell mass is preferentially pooled in the spleen. Patients with myeloid metaplasia may also require ferrokinetic studies to assess the erythropoietic activities in the spleen and bone marrow. Red cell survival and sequestration studies are also indicated in hemolytic anemias associated with splenomegaly and in the auto-immune hemolytic anemias, to determine whether splenectomy will benefit the patient.[6,7] A decidedly shortened ^{51}Cr-red cell survival, associated with progressive accumulation of radioactivity over the spleen, indicates the patient will respond favorably to splenectomy.

During the past few years we have been studying the pathophysiology of thrombocytopenia in various disease states, utilizing the ^{51}Cr-platelet tagging method. Platelets are isolated from one unit of the patient's blood (type specific freshly drawn donor blood is used for isolation of platelets if the patient's platelet count is less than 20,000 per cu mm), labeled with radioactive chromium, washed with autologous plasma, and reinjected into the patient. Blood specimens are taken periodically to establish a platelet survival curve, and surface counts are performed over liver, spleen, and precordium.

In normal volunteers the ^{51}Cr-platelet half-time is approximately four days (Chart 2). Platelet recovery at time zero is 70 percent, as determined by extrapolating the platelet survival curve back to time zero. Thirty percent of platelets are immediately sequestered in the spleen, as reflected by the surface counts. Other investigators report identical findings, and it is our opinion that this 30 percent fraction represents the normal splenic platelet pool.[9-10] After the initial accumulation of splenic radioactivity in normal volunteers, the surface counts over liver and spleen remain more or less stable during the remainder of the platelet survival study.

Representative examples of platelet survival-sequestration studies in patients with acute idiopathic thrombocytopenic purpura (ITP) are

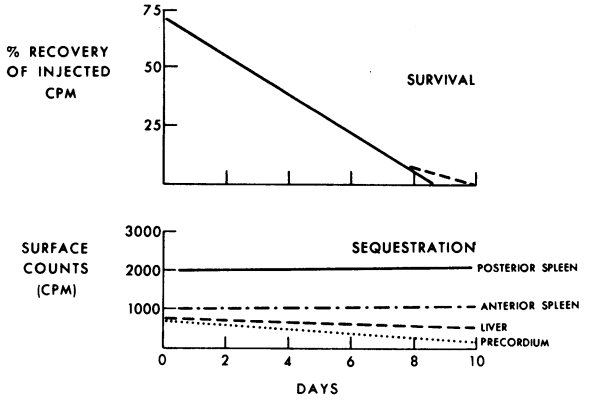

Chart 2.—Study of survival and sequestration of ^{51}Cr-labeled platelets in a normal volunteer. Platelet survival was linear with a $T_{1/2}$ of 4.25 days; platelet recovery at T_0 was 70 percent. Surface counts reflect sequestration of 30 percent of the platelets in the spleen (the normal splenic platelet pool); this "immediate" sequestration occurs within 10 minutes after injection.

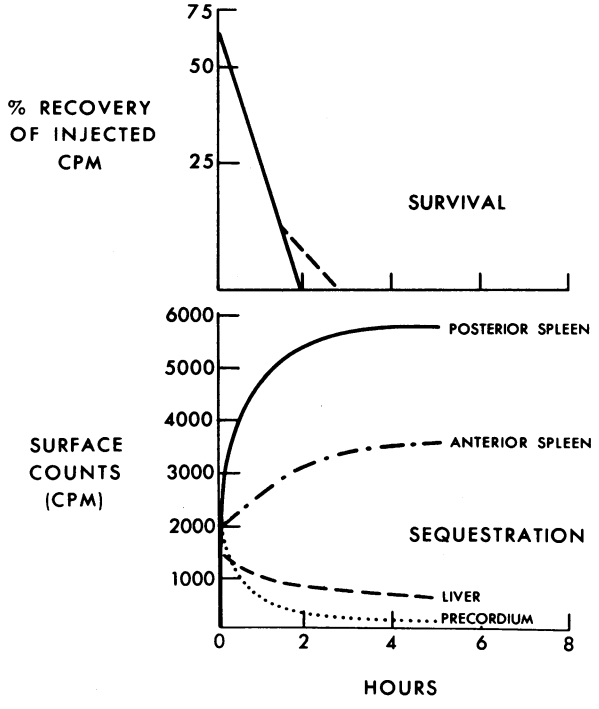

Chart 3.—Platelet survival and sequestration is a patient with acute idiopathic thrombocytopenic purpura and splenic sequestration. Platelet survival was exponential with a $T_{1/2}$ of 1 hour; recovery at T_0 was 70 percent. Surface counts demonstrate progressive splenic sequestration during the platelet survival time. Note that posterior counting over the spleen is much more sensitive than anterior counting for demonstrating splenic sequestration.

shown on Charts 3 and 4. Note that the platelet half-time is extremely short, but the recovery is

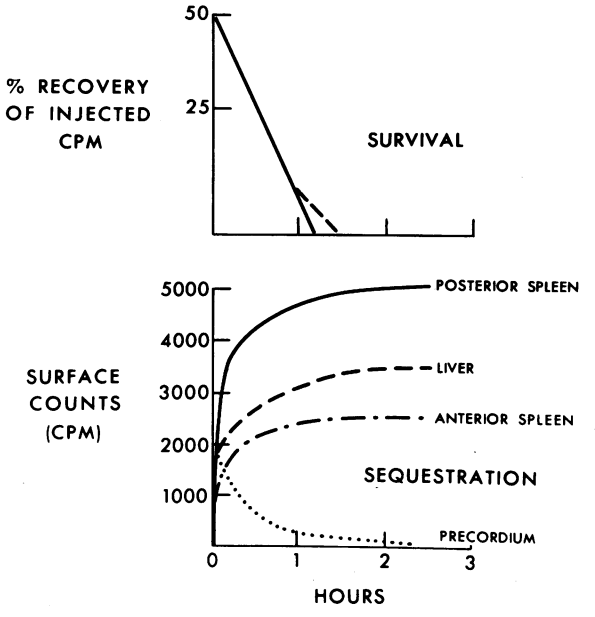

Chart 4.—Platelet survival and sequestration in a patient with acute idiopathic thrombocytopenic purpura and sequestration in both spleen and liver. Platelet survival was exponential with a $T_{1/2}$ of 0.5 hours; recovery at T_0 was 52 percent. Surface counts demonstrate both splenic and hepatic sequestration during the platelet survival time.

essentially normal. The surface counts during the platelet survival time reflect sequestration in the spleen in the first patient, and in both the liver and spleen in the second. The first patient, with splenic sequestration only, had a complete remission after splenectomy, while the second patient, who had both splenic and hepatic sequestration had only partial remission after splenectomy. In our experience with ITP patients, hepatic sequestration does not occur in the absence of splenic sequestration. It is recommended by some investigators that ^{51}Cr-platelet survival-sequestration studies should be done routinely before splenectomy in patients with ITP, in order to predict which ones will have the most successful results.[13] We are accumulating sequestration data on patients with ITP and other forms of thrombocytopenia in an effort to define precise criteria for predicting response to splenectomy.

Patients with thrombocytopenia due to hypersplenism and a markedly enlarged spleen have characteristic platelet kinetics (Chart 5). In contrast to patients with ITP, the abnormality here is one of very low initial platelet recovery. This low recovery is associated with the immediate appearance of very high splenic surface counts,

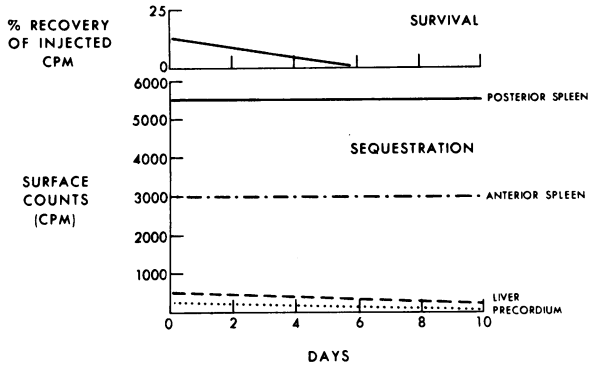

Chart 5.—Platelet survival and sequestration in a patient with hypersplenism caused by congestive splenomegaly (Banti's syndrome). Platelet survival appared to be linear with a $T_{1/2}$ of 3.0 days; platelet recovery at T_0 was 12 percent. The remainder of injected platelets were immediately sequestered in the spleen.

indicating that the normal splenic platelet pool is greatly expanded. In the case illustrated, only 12 percent of the patient's platelets remained in the circulation; the remainder were promptly and preferentially sequestered in the spleen. On the basis of the ^{51}Cr-platelet kinetic data, platelet turnover rates can be calculated to determine whether thrombocytopenia is due to increased destruction, lack of production, or a combination of the two. This kind of information is extremely helpful to the clinician in deciding whether splenectomy should be performed, particularly in patients whose hypersplenism is associated with diseases, such as lymphoma and myelofibrosis that are known to infiltrate the bone marrow.

Technical problems have limited the usefulness of kinetic studies in the evaluation of neutropenic states. Although considerable data have been accumulated on granulocyte kinetics using the DF^{32}p (diisopropyl fluorophosphate) method, this isotope cannot be used for surface counting. While shortened granulocyte survival has been demonstrated in some patients with Felty's syndrome, systemic lupus erythematosus, and cirrhosis associated with splenomegaly, the demonstration of splenic sequestration by radioactivity accumulating over the spleen has not been possible.[14] It seems likely, however, that many patients with these and other diseases do, in fact, have hypersplenism for granulocytes. This is supported by the clinical observations that (a) hyperplasia of the myeloid series is usually present in the bone marrows of these patients, and (b) many of the patients respond to splenectomy.[25] We are hopeful that satisfactory methods for studying granulocyte kinetics, including direct measurement of splenic sequestration, will be available in the near future.

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